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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
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27 January 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PDE4 INHIBITORS FOR THE TREATMENT OF NEOPLASMS OF LYMPHOID CELLS

(57) Abstract: The invention relates to the use of certain PDE4 inhibitors alone or in combination with one or more differentiation inducing agents and/or an agent effective in raising intracellular concentrations of cAMP or a stable analogue of cAMP in the preparation of pharmaceutical compositions for the treatment of neoplasms of lymphoid cells.

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INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/EP2004/000196

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/44 A61K31/4439 A61K31/4709 A61P35/00 A61P35/02
A61K31/502

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01/30777 A (BYK GULDEN LOMBERG CHEM FAB ;STERK JAN GEERT (NL)) 3 May 2001 (2001-05-03) cited in the application the whole document	1-6, 25-30, 50-54, 71-85
Y	WO 02/064584 A (BYK GULDEN LOMBERG CHEM FAB ;GUTTERER BEATE (DE); GRUNDLER GERHARD) 22 August 2002 (2002-08-22) cited in the application the whole document	7-14, 31-38, 55-61, 71-85

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 September 2004	14. 10. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Pacreu Largo, M

INTERNATIONAL SEARCH REPORT

In ›nal Application No
PCT/EP2004/000196

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	REID P: "ROFLUMILAST" CURRENT OPINION IN INVESTIGATIONAL DRUGS, CURRENT DRUGS, LONDON, GB, vol. 3, no. 8, August 2002 (2002-08), pages 1165-1170, XP001119630 ISSN: 0967-8298 the whole document	15-22, 39-47, 62-68, 71-85
Y	SORBERA L A ET AL: "ROFLUMILAST BY-217 3-(CYCLOPROPYLMETHOXY)-N-(3,5-DICHLOROPYRIDIN-4-YL)-4-(DIFLUOROMETHOXY)BENZAMIDE" DRUGS OF THE FUTURE, BARCELONA, ES, vol. 25, no. 12, 2000, pages 1261-1264, XP008016319 ISSN: 0377-8282 table 1	15-23, 39-48, 62-69
Y	BILLAH MOTASIM ET AL: "Synthesis and profile of SCH351591, a novel PDE4 inhibitor" BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 12, no. 12, 17 June 2002 (2002-06-17), pages 1621-1623, XP002297088 ISSN. 0960-894X page 1623	15-18, 39-42, 62-64
Y	NORMAN P: "PDE4 inhibitors: Sustained patenting activity as leading drugs near the market" EXPERT OPINION ON THERAPEUTIC PATENTS 2000 UNITED KINGDOM, vol. 10, no. 9, 2000, pages 1415-1427, XP002235905 ISSN: 1354-3776 abstract page 1423, column 2, paragraph 2	1,7, 15-23, 25,31, 39-48, 83-85
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INTERNATIONAL SEARCH REPORT

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PCT/EP2004/000196

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00/16621 A (LERNER ADAM ;BOSTON MEDICAL CENTER CORP (US)) 30 March 2000 (2000-03-30) page 2, lines 10-20; claim 1 page 3, lines 10-16; examples 3,4,8	1,7,15, 19-23, 25,31, 39, 44-48, 83-85 2-6, 8-14, 16-23, 26-30, 32-38, 40-48, 50-69, 71-85
Y	SIEGMUND B ET AL: "Phosphodiesterase type 4 inhibitor suppresses expression of anti-apoptotic members of the Bcl-2 family in B-CLL cells and induces caspase-dependent apoptosis." LEUKEMIA (BASINGSTOKE), vol. 15, no. 10, October 2001 (2001-10), pages 1564-1571, XP009008175 ISSN: 0887-6924 abstract page 1568 - page 1570	1-3,5-9, 11-17, 19-23, 25-27, 29-33, 35-41, 44-48, 50,51, 53-56, 58-63, 65-69, 71,75, 79,83-85
Y	OGAWA RYOSUKE ET AL: "Inhibition of PDE4 phosphodiesterase activity induces growth suppression, apoptosis, glucocorticoid sensitivity, p53, and p21WAF1/CIP1 proteins in human acute lymphoblastic leukemia cells." BLOOD, vol. 99, no. 9, 1 May 2002 (2002-05-01), pages 3390-3397, XP002235906 May 1, 2002 ISSN: 0006-4971 abstract page 3395, column 2 - page 3396	1,2,4-8, 10-16, 18-23, 25,26, 28-32, 34-40, 42-48, 50, 52-55, 57-62, 64-69, 74,78, 82-85

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INTERNATIONAL SEARCH REPORT

In nal Application No
PCT/EP2004/000196

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KATO G J ET AL: "GROWTH OF ACUTE LYMPHOBLASTIC LEUKEMIA CELLS IS SUPPRESSED BY BETA-1-ADRENERGIC AGONISTS AND THE NOVEL WATER-SOLUBLE FORSKOLIN NKH477" PEDIATRIC RESEARCH, WILLIAMS AND WILKINS, BALTIMORE, MD,, US, vol. 49, no. 4, PART 2, 28 April 2001 (2001-04-28), page 208A, XP009008173 ISSN: 0031-3998 abstract	2,4-6,8, 10-14, 16, 18-23, 26, 28-30, 32, 34-38, 40, 42-48, 50, 52-55, 57-62, 64-69, 74,78, 82-85
Y	KOSUGI H ET AL: "Histone deacetylase inhibitors are the potent inducer/enhancer of differentiation in acute myeloid leukemia: A new approach to anti-leukemia therapy" LEUKEMIA, MACMILLAN PRESS LTD, US, vol. 13, no. 9, September 1999 (1999-09), pages 1316-1324, XP002263859 ISSN: 0887-6924 abstract	2,3,5,6, 8,9, 11-14, 16,17, 19-23, 26,27, 29,30, 32,33, 35-38, 40,41, 44-48, 50, 53-56, 58-63, 65-69, 71-73, 75-77, 79-81, 83-85

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INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/EP2004/000196

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TALLMAN M S: "DIFFERENTIATING THERAPY WITH ALL-TRANS RETINOIC ACID IN ACUTE MYELOID LEUKEMIA" LEUKEMIA, MACMILLAN PRESS LTD, US, vol. 10, 1996, pages S12-S15, XP002915721 ISSN: 0887-6924 abstract	2,3,5,6, 8,9, 11-14, 16,17, 19-23, 26,27, 29,30, 32,33, 35-38, 40,41, 44-48, 50, 53-56, 58-63, 65-69, 71-73, 75-77, 79-81, 83-85
X	WO 01/13953 A (BYK GULDEN LOMBERG CHEM FAB ; KILIAN ULRICH (DE)) 1 March 2001 (2001-03-01) claims	62, 64-69,80
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X	RAEBURN D ET AL: "ANTI-INFLAMMATORY AND BRONCHODILATOR PROPERTIES OF RP 73401 A NOVELAND SELECTIVE PHOSPHODIESTERASE TYPE IV INHIBITOR" BRITISH JOURNAL OF PHARMACOLOGY, BASINGSTOKE, HANTS, GB, vol. 113, no. 4, December 1994 (1994-12), pages 1423-1431, XP000889938 ISSN: 0007-1188 table 6	62,64
X	WO 02/092064 A (MEDICAL RES COUNCIL ; KELLY RODNEY WILLIAM (GB)) 21 November 2002 (2002-11-21) claims 1-4	62,64

INTERNATIONAL SEARCH REPORT

national application No.
PCT/EP2004/000196

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-14,20-23,25-38,45-48,50-61,66-69 and partially 15-19,39-44,62-65,71-85

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-14, 25-38, 50-61 and 71-85 (in part)

Use of compounds of formula 1 or compounds of formula 2 for the manufacture of a medicament for the treatment of neoplasms of lymphoid cells; combinations of compounds of formula 1 or compounds of formula 2 with one or more differentiation inducing agents and/or an agent effective in raising intracellular concentrations of cAMP or a stable analog of cAMP.

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2. claims: 15-19 (in part), 20-23, 39-44 (in part), 45-48, 62-65 (in part), 66-69, 71-85 (in part)

Use of piclamilast, roflumilast, roflumilast-N-oxide, AWD 12-281, AWD 12-343 or SCH-351591 for the manufacture of a medicament for the treatment of neoplasms of lymphoid cells; combinations of piclamilast, roflumilast, roflumilast-N-oxide, AWD 12-281, AWD 12-343 or SCH-351591 with one or more differentiation inducing agents and/or an agent effective in raising intracellular concentrations of cAMP or a stable analog of cAMP.

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3. claims: 15-19 (in part), 24, 39-44 (in part), 49, 62-65 (in part), 70, 71-85 (in part)

Use of V-11294A, CDC-801 or cilomast for the manufacture of a medicament for the treatment of neoplasms of lymphoid cells; combinations of V-11294A, CDC-801 or cilomast with one or more differentiation inducing agents and/or an agent effective in raising intracellular concentrations of cAMP or a stable analog of cAMP.

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4. claims: 15-19, 39-44, 62-65 and 71-85 (all in part)

Use of compound CI-1018 for the manufacture of a medicament for the treatment of neoplasms of lymphoid cells; combinations of compound CI-1018 with one or more differentiation inducing agents and/or an agent effective in raising intracellular concentrations of cAMP or a stable analog of cAMP.

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5. claims: 15-19, 39-44, 62-65 and 71-85 (all in part)

Use of arofylline for the manufacture of a medicament for the treatment of neoplasms of lymphoid cells; combinations of arofylline with one or more differentiation inducing agents and/or an agent effective in raising intracellular concentrations of cAMP or a stable analog of cAMP.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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6. claims: 15-19, 39-44, 62-65 and 71-85 (all in part)

Use of atizoram for the manufacture of a medicament for the treatment of neoplasms of lymphoid cells; combinations of atizoram with one or more differentiation inducing agents and/or an agent effective in raising intracellular concentrations of cAMP or a stable analog of cAMP.

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7. claims: 15-19, 39-44, 62-65 and 71-85 (all in part)

Use of lirimilast for the manufacture of a medicament for the treatment of neoplasms of lymphoid cells; combinations of lirimilast with one or more differentiation inducing agents and/or an agent effective in raising intracellular concentrations of cAMP or a stable analog of cAMP.

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8. claims: 15-19, 39-44, 62-65 and 71-85 (all in part)

The chemical structure of compounds CDC-998, CC-1088, IC-485 and KW4490 is unknown. Therefore, it is not possible to assess if they represent separate inventions or a group of inventions.

INTERNATIONAL SEARCH REPORT

In ɔnal Application No
PCT/EP2004/000196

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Ir onal Application No
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